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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SRIVASTAVA, KAILASH C	
ART UNIT	PAPER NUMBER
1657	

MAIL DATE	DELIVERY MODE
06/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/660,093	MILLER, KENNETH E.	
	Examiner	Art Unit	
	Dr. Kailash C. Srivastava	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11,19 and 21-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,19 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *26.8.2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendment filed 13 March 2007 in response to Office Action mailed 20 October 2006 is acknowledged and entered.

2. Please note, as informed in the Office Action mailed 20 October 2006, the Art Unit Location to which your application has been assigned at the United States Patent and Trademark Office (i.e., USPTO) is Art Unit 1657, not 1616 as noted in the response filed 13 March 2007. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Kailash C. Srivastava in Art Unit 1657.

3. Please also note, upon arrival at the United States Patent and Trademark Office, each response/filing is sorted according to claims, remarks, amendment, transmittal etc. for scanning coding and incorporation in to the Electronic File Wrapper (i.e., IFW). In order to ensure that all the papers pertaining to a particular application are properly coded in the same application electronic file wrapper, and to further facilitate the prosecution; especially during a telephonic conversation/interview with applicant/applicants' representative, it is urged that the following information be recited not only on the first page of the response but also in the header of each page for any filing/response/amendment:

a. Attorney Docket Number;
b. First Applicant's name (e.g., Smith Jones et al.);
c. Filing date for said application (e.g., 17 November 2002);
d. U.S. Non-Provisional Application Serial Number (e.g. 00/000,000);
e. Group Art Unit Number (e.g., 1657);
f. Date of Office Action being responded to (e.g., 27 August 2006);
g. Date of amendment/response (e.g., 27 April 2007); and
h. Examiner's name (e.g., Dr. Kailash C. Srivastava);

Papers/responses filed according to above-stated guidelines immensely ameliorate the chances of papers lost during transaction/transmission, coding, indexing and placing the papers in IFW.

CLAIMS STATUS

4. Claims 2, 12-18 and 20 have been cancelled.

5. Claims 1, 3-11, 19, 21 and 23 have been amended.

6. Claims 1, 3-11, 19 and 21-23 are pending.

Restriction/Election

7. Election of Group I, Claims 1, 3-11,19 and 21-23 readable thereon filed 13 March 2007 in response to Office Action mailed 20 October 2006 is acknowledged and entered. Because said election has not been distinctly and specifically traversed, said election has been treated as an election without traverse (MPEP § 818.03(a)). Accordingly, the restriction requirement is deemed proper and is made FINAL.

8. Claims 1, 3-11, 19 and 21-23 are examined on merits.

Information Disclosure Statement

9. The Information Disclosure Statement (i.e., IDS) filed 26August 2004 has been made of record and considered

Priority

10. Claim for domestic priority under 35 U.S.C. §119(e) to Provisional U.S. Application Serial Numbers 60/318,861 filed 13 September 2001 and to 60/411, 311 filed 13 September 2002 is acknowledged.

11. Claim for domestic priority under 35 U.S.C. §121 to non-Provisional U.S. Application Serial Number 10/245,098 filed 13 September 2002 is acknowledged.

Objection To Claims – Minor Informalities

12. Claims 7-8 and 22-23 objected to because of the informality of lacking insertion at Line one of each one of the cited Claims, a --, -- before the word "wherein".

Appropriate correction is required.

Claim Rejections - 35 U.S.C. §112

13. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> ***The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.***

14. Claims 1, 3-11, 19 and 21-23 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims are drawn to a method to alleviate chronic or chronic and acute pain at a subject's peripheral nervous system inflammation site via administering to said site of said individual an effective amount of an inhibitor of neurotransmitter synthesis. Said inhibitor is selected from the group consisting of a glutamine synthetase inhibitor, a glutamate dehydrogenase inhibitor, a pyruvate carboxylase inhibitor, a glutamine cycle inhibitor, a glial cell tricarboxylic acid cycle inhibitor or combination thereof. Said administration results in reducing nociceptive responses at said site. Said neurotransmitter synthesis inhibitor is one among: phenyl acetic acid (i.e., PAA), phenylacetyl Coenzyme A, phenylacetyl Coenzyme A ester, oxamate, meethionine-s-sulfoximine (i.e., MSO), phosphinothricin (i.e., PPT), 4-N-hydroxy-L-2, 4-diaminobutyric acid (i.e., NH-DABA, Delta-hydroxylysine (i.e., DHL), bromofuroate, Palmitoyl –Co enzyme A (i.e., Co-A, orthovanadate, vanadyl sulphate, vanadyl acetylacetonate, glutarate, 2-oxoglutarate, estrogen, estrogen analogues, pyridine-2, 6-dicarboxylic acid, fluroacetate, flurocitrate and combinations and derivatives thereof.

From the record of the present disclosure, however, the specification, while enabling for alleviating the chronic pain in an individual via administering a glutaminase inhibitor to said individual does not provide information on inhibition of glutaminase enzyme synthesis
by said step. Also, the specification as currently presented, apart from merely mentioning, does not disclose oral administration of said glutaminase inhibitor. Specification as currently presented, merely shows a statement that "One specific example of a compound functioning in this manner is dicoumarol (DC), which is shown herein to inhibit ZC activity and thus inhibit GT production, thereby relieving pain. Therefore, the terms "glutaminase inhibitor", "inhibitor of glutaminase enzyme activity" and "inhibitor of glutaminase synthesis" can all be used interchangeably herein" (Specification, Page 18, Line 15 to Page 19. Line 7; Page 19, Line 15 to Page 20, Line 14). The specification also describes "dicoumarol, a ZC inhibitor, disrupts increased glutaminase production during chronic inflammation" and figure 15 illustrates it (Page 13, Lines 8-11). However, in said Figure the glutaminase concentration or production thereof is not even shown.

Thus, specification as currently presented while enabling for alleviating the chronic pain in the peripheral nervous system of a subject via administering a glutaminase inhibitor to said individual does not provide information on inhibition of glutaminase enzyme production by said step, nor said effect is

achieved through oral administration for said glutaminase inhibitor. Therefore, as currently presented, the specification does not provide for one of skill to practice the claimed invention.

A person of ordinary skill would not be able to practice the invention because undue experimentation will be required to obtain a method to inhibit glutaminase production via orally administering an inhibitor of glutaminase enzyme activity to said individual due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as illustrated below.

(a) Quantity of Necessary Experimentation

Since the specification does not provide any evidence on how the glutaminase enzyme activity inhibitor will inhibit the glutaminase enzyme production, an artisan of ordinary skill will have to perform a number of permutations and combinations to obtain conditions to establish whether said glutaminase enzyme activity inhibitor also inhibits the production of said glutaminase enzyme.

(b) Limited Amount of Guidance

The specification as currently presented does not provide a clear-cut guidance to obtain the claimed information that said glutaminase enzyme activity inhibitor also inhibits the production of said glutaminase enzyme.

(c) Limited Number of Working Examples in the Specification

The specification does not provide any specific example to determine that said glutaminase enzyme activity inhibitor also inhibits the production of said glutaminase enzyme.

(d) Nature of the Invention

The invention is particularly drawn to a method to alleviate chronic pain in an individual via administering a glutaminase enzyme activity inhibitor to said individual, wherein said administration is also by oral route among others and said glutaminase enzyme activity inhibitor also inhibits the production of glutaminase enzyme.

(e) State of the Prior Art

The prior art is silent about the inhibition of production of glutaminase enzyme by an inhibitor of glutaminase enzyme activity

(f) Relative Skill Level of those in the Art

At least a Degree in Biochemical engineering, Biochemistry, Biology, Biomedical engineering, Biophysics, Chemical engineering, Chemistry, Medicine, Microbiology, Molecular biology, Pharmaceutical Sciences, or Pharmacology.

(g) Predictability or Unpredictability in the Art

Unless supported with illustrative experimental evidence, biological responses are unpredictable. Thus, information obtained under one set of detrimental parameters may not be extrapolated for another set of parameters/environmental or specific conditions.

(h) Breadth of the Claims

The claimed invention is drawn upon claims that are not supported by the presently detailed specification.

15. Claims 1, 3-11, 19 and 21-23 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with those claims. The claimed invention is drawn to a method to alleviate chronic pain in an individual via administering to said individual an inhibitor of the glutaminase enzyme activity or an inhibitor of glutaminase enzyme production, wherein said inhibitor is orally administered to said individual.

From the record of the present disclosure, however, the specification, while enabling for alleviating the chronic pain in the peripheral nervous system of an individual via administering a glutaminase inhibitor to said individual does not provide information on oral administration of said glutaminase inhibitor.

A person of ordinary skill would not be able to practice the invention because undue experimentation will be required to obtain a method to inhibit glutaminase production via orally administering an inhibitor of glutaminase enzyme activity to said individual due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art;

predictability or unpredictability in the art; and breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as illustrated above.

Rejection Under 35 U.S.C. §112, Second Paragraph

16. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> ***The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.***

17. Claims 3 and 21 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claims 3 and 21 depend from the cancelled claims 2 and 20 respectively and are, therefore, also rejected under 35 U.S.C. §112, second paragraph for the reasons set forth above.

- The recitation, "derivatives" in claims 3 and 21 is unclear as well as confusing, and therefore indefinite because said recitation does not clearly define degree of similarity of claimed compound to the base compound to be called derivative of a base compound, i.e. the term does not define the metes and bounds of the claimed subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

19. Claims 1, 3-11, 19 and 21-23 are rejected under 35 U.S.C. § 103(a) as obvious over the combined teachings from Rosenberg (U.S. Patent 5,158,976) with evidence provided by Melzack et al. (Pain Mechanisms: A New Theory, Science, Volume 150, Number 3699, 19 November 1965, Pages 971-979) and further in view of Fujimoto et al (U.S. Patent 6,291,523).

Claims 1, 3-11, 19 and 21-23 recite a method to alleviate chronic or chronic and acute pain at a subject's peripheral nervous system inflammation site via administering to said site of said individual an

effective amount of an inhibitor of neurotransmitter synthesis. Said inhibitor is selected from the group consisting of a glutamine synthetase inhibitor, a glutamate dehydrogenase inhibitor, a pyruvate carboxylase inhibitor, a glutamine cycle inhibitor, a glial cell tricarboxylic acid cycle inhibitor, and combination thereof. Said administration results in reducing nociceptive responses at said site. Said neurotransmitter synthesis inhibitor is one among: phenyl acetic acid (i.e., PAA), phenylacetyl Coenzyme A, phenylacetyl Coenzyme A ester, oxamate, meethionine-s-sulfoximine (i.e., MSO), phosphinothricin (i.e., PPT), 4-N-hydroxy-L-2, 4-diaminobutyric acid (i.e., NH-DABA, Delta-hydroxylysine (i.e., DHL), bromofuroate, Palmitoyl –Co enzyme A (i.e., Co-A, orthovanadate, vanadyl sulphate, vanadyl acetylacetonate, glutarate, 2-oxoglutarate, estrogen, estrogen analogues, pyridine-2, 6-dicarboxylic acid, fluroacetate, flurocitrate and combinations and derivatives thereof.

Regarding Claims 1, 3-11, 19 and 21-23, Rosenberg conceptually teaches a method to treat diseases involving neuronal death via administering inhibitors of glutaminase converting enzyme activity either alone or in mixture with more than one glutaminase inhibitors (Column 8, Lines 15-52), wherein said administration may or may not pass across the blood brain barrier (Column 8, Lines 31-33). Rosenberg further teaches methods of administering said inhibitors to treat neuronal injury/death via administering to an individual in need thereof an inhibitor of enzymatic conversion of glutamine to glutamate (Abstract; Column 1, Lines 44-67; Column 8, Lines 27-31) and also teaches that effect of said inhibitors is tested *in vivo* to evaluate the effect of said inhibitors in subjects having neuronal-injury related conditions via evaluating the effects on peripheral sites through histological examination (Column 7, Lines 34-51). Note that nociceptive pain behavior is a manifestation of neuronal injury (See Melzack and Wall's gate control theory in Science 1965 Said theory suggested that when body tissues are damaged, messages carrying information about the injury travel toward the brain along two separate sets of nerve fibers. The larger (mechanoreceptive) fibers transport messages about sensations other than pain (joint movement, heat, touch, etc.), and the smaller (nociceptive) fibers carry the pain signals) Rosenberg further teaches methods to evaluate glutaminase inhibition with glutaminase inhibitors *in-vitro* and *in-vivo* (Example 2). Rosenberg does not explicitly teach alleviation of chronic pain upon administration of glutaminase inhibitors, however, neuronal injury and death would also result in pain as explained above. Since Rosenberg teaches methods to treat diseases symptomatic of neuronal injury/death (Column 8, Lines 23-26); intrinsically Rosenberg is teaching methods to alleviate chronic and acute pain in subjects via administering through different administering modes including oral administration as well as spinal tap (Column 8, Lines27-33). Note that spinal tap is a means of administering a therapeutic agent at a peripheral inflammation site.

Thus, Rosenberg intrinsically teaches amelioration of chronic/acute pain in an individual because administration of one of the glutaminase inhibitors according to the method steps described in the prior art method (i.e., Rosenberg) intrinsically must function as claimed because the said prior art composition is comprised of a glutaminase inhibitor and is being administered in the same way as the claimed method (See e.g., In re Best, 195 USPQ 430, 433-CCPA 1977). Also, note that administration of glutaminase inhibitor resulting in a reduction in nociceptive response at a site of inflammation is not the net result- merely a mechanism whereby acute and or chronic pains are reduced/ inhibited in an individual administered with said glutaminase inhibitor and therefore does not carry any patentable weight.

Fujimoto et al. teach a method to treat inflammation and pain in a mammal via administering a composition comprising a compound of phenyl acetic acid, which also is an inhibitor of neurotransmitter synthesis (Column 1, Lines 13-22; Column 1, Line 65 to Column 2, Line 25). Note that applicant admits on record that the claimed invention relates to alleviating pain by regulation of neurotransmitter synthesis (Page 2, Lines7-9). Thus, intrinsically Fujimoto et al. teach treating pain via administering a glutaminase inhibitor.

One having ordinary skill in the art at the time of the claimed invention would have been motivated to modify/combine the teachings from Fujimoto et al. with those from Rosenberg; because Fujimoto et al. teach ameliorating pain in a subject via administering to said individual a neurotransmitter inhibitor, wherein said inhibitor is a phenyl acetic acid compound. As illustrated above, Rosenberg conceptually teaches administering a glutaminase inhibitor to a subject to alleviate neuronal injury that is manifested by pain by spinal cord tapping.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify Rosenberg's teachings via incorporating Fujimoto et al's teachings to alleviate chronic/acute pain in a subject via administering to said subject a neurotransmitter synthesis inhibitor, wherein said inhibitor is a glutamianse inhibitor (e.g., a phenyl acetic acid compound).

From the teachings of the references cited *supra*, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In this rejection under 35 U.S.C. §103(a), Melzack et al. (Pain Mechanisms: A New Theory, Science, Volume 150, Number 3699, 19 November 1965, Pages 971-979) is cited to merely support that the nociceptive pain behavior is a manifestation of neuronal injury, and not as a prior art reference.

Conclusion

20. For reasons aforementioned, no Claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached at (571)-272-0925 Monday through Thursday 7:30 A.M. to 6:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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May 26, 2007

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